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SYNTHESIS AND STRUCTURE OF DITIOCARBAMATES BASED ON THE ALKALOID CITIZIN

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By the interaction of the cytisine alkaloid with carbon disulfide in the presence of alkali metals (potassium and sodium) and ammonia, the alkali, amine and ammonium salts of alkaloid dithiocarbamic acid are synthesized. Using modern physicochemical methods of analysis (IR, NMR1H spectroscopy), the structure of the synthesized compounds was established.

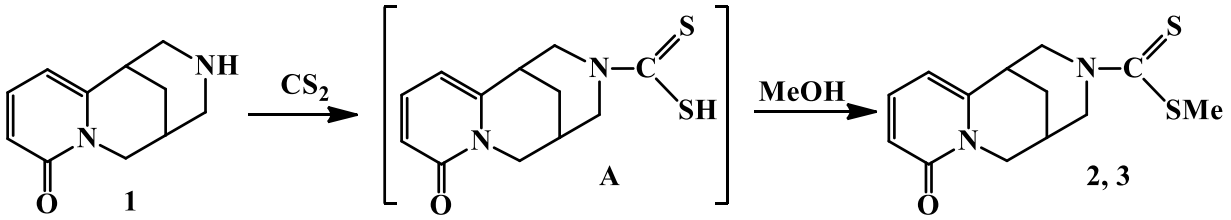
Key words: alkaloid cytisine, carbon disulfide, alkali metals, ammonium salts, dithiocarbamates, NMR spectra.

Dithiocarbamates compounds in whose molecules the carbodithium group is bonded to the nitrogen atom $R_2NC(S)SH$ are one of the most common sulfur-containing compounds in organic chemistry. Numerous scientific publications [1-3] indicate special attention of synthetic chemists to various derivatives of dithiocarbamides new acid, which is associated with their high reactivity, as well as their unique physiological, acid-base, redox and complexing properties.

In this regard, it seems very interesting to study the possibilities of introducing a carbodithium group into the structure of a natural bioactive substance, which can lead to a decrease in toxicity and an increase in the physiological activity of the initial substrate. Alkaloid derivatives of dithiocarbamic acids contain in one molecule a physiologically active heterocyclic framework of an optically active natural substance and a highly reactive dithium group. Such a combination of fragments will correspond to the “ δ-rule " [4], i.e. the mutual arrangement of their pharmacophore sites in their molecules should sometimes give compounds unexpected properties and go beyond the traditional synthetic potential, consisting of the known properties of these fragments. One of the interesting alkaloids is cytisine, which was first isolated from the seeds of thermopsis (Termopsis lanceolata) and is widely used in medical practice (the drug “cytitone”) to stimulate respiration and enhance cardiac activity during intoxication [5]. Due to the presence in the structure of the system of conjugated double bonds, a secondary amino group, and an amide function, which are fragments

of a volume molecule consisting of three cycles joined together, cytisine (1) continues to attract the attention of synthetic chemists.

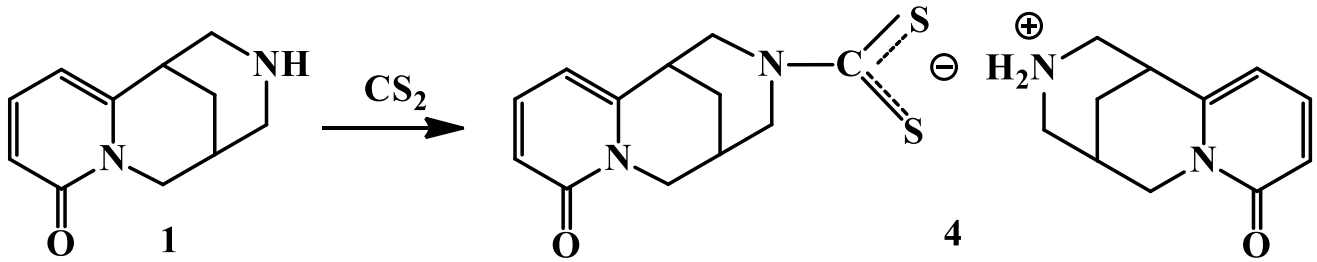
In this regard, we synthesized a number of new dithiocarbamate salts of cytisine and established their structures. Dithiocarbamate salts (sodium and potassium) (2, 3) of cytisine were prepared as follows. The calculated amount of the corresponding alkali metal hydroxide was dissolved in 3-5 ml of water and mixed with a benzene solution of carbon disulfide. Under vigorous stirring and cooling, a benzene alkaloid solution was added dropwise to the mixture and stirred for one hour. The resulting white crystals (2, 3) were filtered off on a glass filter and washed several times with benzene. The yields of the target products (2, 3) were 93 and 95%, respectively. It should be noted that recrystallization from ethanol-water mixture leads to the formation of crystalline hydrates.



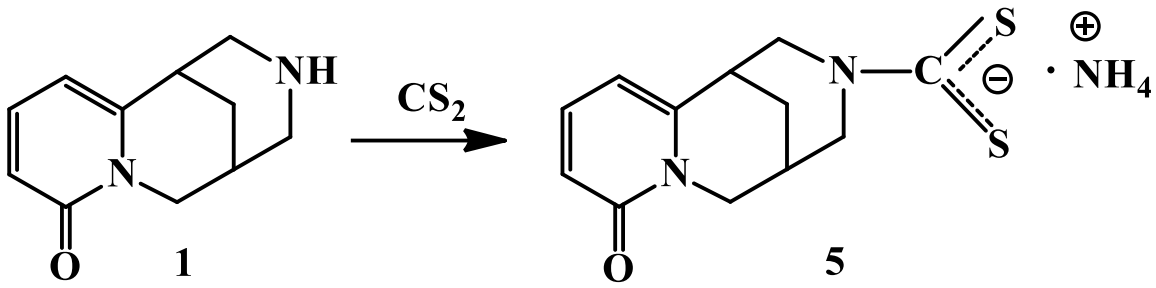
Me = K (2), Na (3).

The reaction proceeds through the stage of formation of cytisinyl dithiocarbamic acid (A); in the absence of alkali in the solution, an amine salt, slightly soluble in water, is formed cytisinium cytisinyl dithiocarbamate (4).

Cytisine cytisinyl dithiocarbamate (4) was obtained by the interaction of a benzene solution of cytisine with carbon disulfide. The reaction was carried out with stirring and cooling of the reaction medium. Immediately observed the formation of white flocculent crystals, which at the end of the reaction were filtered and washed with dry ether. The yield of product (4) was 98%, so pl. 150°C (decomp.).



Ammonium cytisinyl dithiocarbamate (5) is formed by the interaction of strictly equivalent amounts of carbon disulfide and cytisine dissolved in ethanol, saturated (with excess) with gaseous ammonia.



The reaction was carried out while cooling the reaction medium with ice and salt (0–3°C). The yield of the target product was 93%, so pl. 147-148°C. A comparative analysis of the experimental results showed that the amine salts of cytisine dithiocarbamates are obtained in higher yields and pure. All synthesized salts are stable when stored in air.

The structure of the obtained dithiocarbamates (2-5) was proved by NMR1H and IR spectroscopy. In the IR spectra of compounds (2-5), the most characteristic strong absorption is observed in the region of 1540-1480 cm 1. Its appearance in a number of works is associated with vibrations of the thioureid group [6, 7]. Absorption in the region of 1250–1200 cm 1 is due to stretching vibrations of the N-C- group, and absorption in the region of 1175–1145 cm 1 is due to characteristic vibrations of the dithiocarbamate group [8]. Absorption at 876–790 cm 1 is usually attributed to vibrations of the C – S bond in dithiocarbamic acid derivatives [9]. The stretching vibrations of the lactonic C = O group of the compound (72-75) are manifested at 1690-1720 cm 1.

In the NMR ^{1}H spectra of compounds (2-5), the protons of the alkaloid framework in dithiocarbamate resonate in the spectral regions characteristic of them. So, three groups of low-field signals correspond to protons of the α-pyridine nucleus. Signals at 7.20 ppm correspond to the H_2 proton with the spin-spin coupling constant J_{H2H3} = 8.0 Hz. Split doublet at 6.32 ppm - proton H_1 with J_{H1H2} = 10.0 Hz. The next group of lines, which is a complex multiplet in the region of 3.20–4.40 ppm, corresponds to axial and equatorial protons in position C_7. The signals of the H_8 protons are split in the region of 2.38 ppm. (doublet). The group of lines in the region of 2.98-3.10 ppm represents signals of H_4, H_6 protons. Methylene protons H_5 manifest themselves in the form of a complex multiplet in the region centered at 1.96 ppm. [10]. When comparing spectrum (4) and the initial alkaloid cytisine (1), a shift of proton signals at C_8 and C_8 ’is observed. This, apparently, is due to the fact that the unshared pair of electrons (NPE) of the neighboring nitrogen atom N, occupying the equatorial position in cytisine, when the hydrogen atom is replaced by a more complex radical, becomes axial. Due to this, it becomes possible to delocalize the NPE to the loosening orbital of the CH bond, which leads to an increase in the screening of these protons.

Experimental part.

The IR spectra of the synthesized compounds were recorded on an AVATAR-320 spectrometer in a thin layer, in tablets with KBr, in solutions of chloroform and carbon tetrachloride (measurement error 0.2 cm 1).

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer with an operating frequency of 300 MHz in DMSO-d6 solutions at room temperature relative to the internal standard (HMDS).

The melting temperature was determined on a Boetius instrument (measurement error □ 0.1 ° C).

Potassium salt of cytisinyl dithiocarbamic acid (2). 0.84 g (0.015 mol) of potassium hydroxide dissolved in a minimum amount (3-5 ml) of water was added to 1.9 g (0.01 mol) of cytisine. With cooling (t = 2 ÷ 50 ° C) and stirring, 0.7 ml (0.011 mol) of carbon disulfide was added dropwise to the reaction mixture. After removing water, the precipitate was dissolved in acetone (or alcohol) and precipitated with ether. Recrystallization from ethanol gave a colorless crystalline solid, mp. 215°C (decomp.). The yield of salt (2) was 2.73 g (95%).

The sodium salt of cytisinyl dithiocarbamic acid (3) was obtained analogously to compound (2). Got a white crystalline substance with so pl. 216°C (decomp.). The yield of salt (3) was 2.82 g (93%).

Cytisine cytisinyl dithiocarbamate (4). In a stirred benzene solution, 1.9 g (0.01 mole) of cytisine was slowly added dropwise from a dropping funnel 0.7 ml (0.011 mole) of carbon disulfide. The resulting white flaky powder was filtered on a Schott funnel and washed several times with ethyl ether. After recrystallization from ethanol, a white powder was obtained with a mp of 150 ° C (decomp.), The yield of which was 98%.

Ammonium salt of cytisine dithiocarbamate (5). Ethyl alcohol was saturated with ammonia for 4 hours. After 1 g (0.005 M) of cytisine was dissolved, 0.4 g (0.005 M) of carbon disulfide was added with slight cooling. It was further stirred at room temperature for 7 hours. The solvent was distilled off. Received 1.03 g (73.6%) of crystalline substance with a mp of 169-170 ° C.

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